DETAILED ACTION

Status of the Claims

1. Claims 67-83 and 85 are pending.

Applicants' response filed June 2, 2010 is acknowledged. Applicants' response has been fully considered. Therefore, claims 67-83 and 85 are examined.

Withdrawn Claim Objections

2. The previous objection to claims 70-75, 77, 78, 80-83 and 85 is withdrawn in view of applicants' submission of a terminal disclaimer, and applicants' response at page 5 of the amendment filed June 2, 2010.

Withdrawn Claim Rejections-Obviousness Type Double Patenting

3. The previous rejection of claims 67-69, 76 and 79 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 of U.S. Patent 6,743,769, is withdrawn in view of applicants' submission of a terminal disclaimer, and applicants' response at page 5 in the amendment filed June 2, 2010.

4. The previous rejection of claims 67-69, 76 and 79 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent 7,067,621, is withdrawn in view of applicants' submission of a terminal disclaimer, and applicants' response at page 5 in the amendment filed June 2, 2010.

Examiner's Amendment

An **Examiner's Amendment** to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Examiner's Amendments to the Specification:

-Please replace the title at page 1, line 1 of the specification with the following title:

ANTIMICROBIAL PEPTIDES AND DERIVED METAPEPTIDES

-Please replace the paragraph at page 1, lines 3-8 with the following paragraph:

RELATED APPLICATIONS:

This application is a continuation-in-part of U.S. Patent Application No. 09/622,561, filed October 6, 2000, now abandoned, which is a 371 of PCT/US99/03350, filed February 17, 1999, which is a continuation-in-part of U.S. Patent Application No. 09/025,319, filed February 18, 1998, now abandoned. All of which applications are incorporated by reference in their entirety.

-Please replace the phrase at page 2, line 1 with the following phrase:

because microbicidal peptides appear to target the cytoplasmic membrane or other essential

-Please replace the phrase at page 3, line 1 with the following phrase:

from platelets stimulated with agonists associated with infection. Therefore, in response to

-Please replace the phrase at page 4, line 1 with the following phrase:

SUMMARY OF THE INVENTION

-Please replace the phrase at page 5, line 1 with the following phrase:

or derived metapeptide of the invention can further comprise a retromeric sequence of

-Please replace the phrase at page 6, line 1 with the following phrase:

fusions, and derivatives thereof, the peptide having antimicrobial activity. Within one

-Please replace the phrase at page 7, line 1 with the following phrase:

selected from the group consisting of lysine, arginine and histidine; aa_{10} is selected from

-Please replace the phrase at page 8, line 1 with the following phrase:

terminus of the peptide and is selected from the group consisting of leucine, isoleucine,

-Please replace the phrase at page 9, line 1 with the following phrase:

antimicrobial peptide further comprises a pharmaceutically acceptable carrier. Within

-Please replace the phrase at page 10, line 1 with the following phrase:

group consisting of leucine, isoleucine, alanine, valine, serine, glycine, and threonine; aa_3

-Please replace the phrase at page 11, line 1 with the following phrase:

arginine and histidine; aa_6 is cystine; aa_7 is selected from the group consisting of threonine

-Please replace the phrase at page 12, line 1 with the following phrase:

With another aspect of the invention antimicrobial peptides are provided

-Please replace the phrase at page 13, line 1 with the following phrase:

acid core sequence domain are separated by an amino acid selected from the group

-Please replace the phrase at page 14, line 1 with the following phrase:

alanine, aa_2 is asparagine, aa_3 is serine, aa_4 is glycine, aa_5 is glutamic acid, aa_6 is glycine,

-Please replace the phrase at page 15, line 1 with the following phrase:

valine, serine, glycine, threonine, phenylalanine, tryptophan, tyrosine, lysine, arginine,

-Please replace the phrase at page 16, line 1 with the following phrase:

acid sequence domain, and a fourth amino acid sequence domain, wherein the first amino

-Please replace the phrase at page 17, line 1 with the following phrase:

leucine. Within another embodiment the amino acid core sequence further contains the

-Please replace the phrase at page 18, line 1 with the following phrase:

Within another aspect of the invention antimicrobial peptides are provided

-Please replace the term "(ADSGEGDFLAEGGGVR)" at page 18, line 14 with the term "(ADSGEGDFLAEGGGVR, SEQ ID NO:25)".

-Please replace the term "(EGVNDNEEGFFSA)" at page 18, line 14 with the term "(EGVNDNEEGFFSA, SEQ ID NO:27)".

-Please replace the phrase at page 19, line 1 with the following phrase:

of D- or other unusual amino acids into the peptide templates and derivative metapeptide

-Please replace the phrase at page 20, line 1 with the following phrase:

Fig. 7 is a two-dimensional graph of the antimicrobial spectra of the mean

-Please replace the term "PMP-2" at page 20, line 16 with the term "PMP-2 (SEQ ID NO:1)".

-Please replace the term "RP-1;" at page 20, line 24 with the term "RP-1 (SEQ ID NO:3);".

-Please replace the term "RP-13;" at page 20, line 26 with the term "RP-13 (SEQ ID NO:14);".

-Please replace the phrase at page 21, line 1 with the following phrase:

Fig. 23 is a summary of the RP-13 in vitro spectrum of activity and potency;

-Please replace the phrase at page 22, line 1 with the following phrase:

PMPs have structure-function correlates that optimize antimicrobial activity relative to

-Please replace the phrase at page 23, line 1 with the following phrase:

Thus, these peptides will additionally significantly advance our understanding of molecules

-Please replace the phrase at page 24, line 1 with the following phrase:

neutrophil chemotaxis and microbicidal activity in vitro. The fact that PMD-2 (Sequence

-Please replace the phrase at page 25, line 1 with the following phrase:

have now isolated and characterized rabbit and human PMPs that likely significantly

-Please replace the phrase at page 26, line 1 with the following phrase:

elaborated in the setting of endovascular infection. Fractions of these preparations were

-Please replace the phrase at page 27, line 1 with the following phrase:

or C. albicans infection. In the rabbit model, PMP^{S} C. albicans exhibits significantly less

-Please replace the phrase at page 28, line 1 with the following phrase:

Compositional analyses reveal that PMPs and tPMPs contain high proportions of basic

-Please replace the phrase at page 29, line 1 with the following phrase:

PMPs and tPMPs target and disrupt microbial cytoplasmic membranes. We

-Please replace the phrase at page 30, line 1 with the following phrase:

variable-cystine (C-X-C) motif characteristic of the α-chemokines integral to neutrophil

-Please replace the phrase at page 31, line 1 with the following phrase:

Therefore, the mechanism of PMP-2 action involves rapid, pH-dependent membrane

-Please replace the phrase at page 32, line 1 with the following phrase:

PMP-2 exhibits sequences homologous to chemokine and microbicidal

-Please replace the phrase at page 33, line 1 with the following phrase:

approaches: we have identified, synthesized, purified, and evaluated a microbicidal domain

-Please replace the phrase at page 34, line 1 with the following phrase:

a model candidate. After minimization, all models were similar, with <1 Å rms difference

-Please replace the phrase at page 35, line 1 with the following phrase:

It is important to note convergence of the predicted and determined PMP-

-Please replace the phrase at page 36, line 1 with the following phrase:

the SYBYL algorithm DOCK. Molecular mechanics and molecular dynamics can then be

-Please replace the phrase at page 38, line 1 with the following phrase:

rapidly. Equilibrium can be defined as lack of at detectable difference in measurements of

-Please replace the phrase at page 39, line 1 with the following phrase:

recorded at an accelerating voltage of 16 kV at 16000 nanosecond intervals, and analyzed

-Please replace the phrase at page 40, line 1 with the following phrase:

various animal models. Strain pain such as these are also crucial to future studies to define

-Please replace the phrase at page 41, line 1 with the following phrase:

proteolytic degradation than comparable larger proteins. Thus truncated analogues of

-Please replace the phrase at page 42, line 1 with the following phrase:

4. Retromer Peptides: Stereo-specificity likely plays an important role

-Please replace the phrase at page 43, line 1 with the following phrase:

then be measured and compared. The reduced peptide provides a control on possible

-Please replace the phrase at page 44, line 1 with the following phrase:

65:1023-1031, 1997. In turn, these or other microbicidal peptides can also be used

-Please replace the phrase at page 45, line 1 with the following phrase:

hydrophobic domain. The above model has been refined to integrate M_H and α-helical or

-Please replace the phrase at page 46, line 1 with the following phrase:

With reference to Figs. 2A and 2B, designs for novel microbicidal

-Please replace the phrase at page 47, line 1 with the following phrase:

$^{\varepsilon}$monomethyl-lysine and/or D-amino acid analogues. These strategies can be useful to

-Please replace the phrase at page 48, line 1 with the following phrase:

conformation in relationship to lipid interaction. The environment of the lipid bilayer can

-Please replace the phrase at page 49, line 1 with the following phrase:

synthetic step. Thus each bead carries a record of the synthesis of the compound also

-Please replace the phrase at page 50, line 1 with the following phrase:

phases such as PRP-300 (Hamilton) used lo purify crude peptides on a preparative scale.

-Please replace the phrase at page 51, line 1 with the following phrase:

Antibiotic Resistance Phenotype

-Please replace the phrase at page 52, line 1 with the following phrase:

purified by RP-HPLC lacking antimicrobial activity are tested in parallel as controls.

-Please replace the phrase at page 53, line 1 with the following phrase:

Organisms are resuspended to a concentration of 5 x $l0^8$ CFU/ml in K^+MEM containing an

-Please replace the phrase at page 54, line 1 with the following phrase:

endothelial cells in 96 well tissue culture plates are incubated with $Na^{51}CrO_4$ overnight.

-Please replace the phrase at page 55, line 1 with the following phrase:

Alpha-chemokines such as PF-4 and IL-8 are critical in amplifying the host

-Please replace the phrase at page 56, line 1 with the following phrase:

domains found to amplify phagocytosis or intracellular killing by neutrophils can be

-Please replace the phrase at page 57, line 1 with the following phrase:

influence neutrophil antimicrobial function via the CXCR1 or CXCR2 receptor. Rabbit

-Please replace the phrase at page 58, line 1 with the following phrase:

reverse direction, artificially reducing peptide-mediated neutrophil chemotaxis. Neutrophil

-Please replace the phrase at page 59, line 1 with the following phrase:

Additionally, peptide analogues can be achieved using a combinatorial

-Please replace the phrase at page 60, line 1 with the following phrase:

labeled neutrophils are readily distinguishable from BCECF-labeled microorganisms.

-Please replace the phrase at page 61, line 1 with the following phrase:

performed microscopically to confirm flow cytometric data. These controls allow us to

-Please replace the phrase at page 62, line 1 with the following phrase:

effect. The generation of reactive oxygen intermediates such as superoxide anion is

-Please replace the phrase at page 63, line 1 with the following phrase:

These groups are described in the application; they are not

-Please replace the phrase at page 64, line 1 with the following phrase:

21-K,ELR-PMP-2_{1-22}: Ser Asp Asp Pro Lys Glu Ser Glu Gly Glu Leu Arg Cys Val Cys Val

-Please replace the phrase at page 65, line 1 with the following phrase:

RP-1/PMP-2_{1-22}: Ala Leu Tyr Lys Lys Phe Lys Lys Lys Leu Leu Lys Ser Leu Lys

-Please replace the phrase at page 66, line 1 with the following phrase:

glycine, methionine, serine and threonine, may be interplaced within these primary

-Please replace the phrase at page 67, line 1 with the following phrase:

testing for toxicity, structure and antimicrobial activity, to identify promising candidates

-Please replace the phrase at page 68, line 1 with the following phrase:

Another novel effective antimicrobial peptide that is a truncation fragment

-Please replace the phrase at page 69, line 1 with the following phrase:

C. Combination/fusion Example:

-Please replace the phrase at page 71, line 1 with the following phrase:

Ala Thr Lys Lys Asn Gly Arg Lys Leu Cys Leu Lys Ser Leu Lys Arg Leu Gly

-Please replace the phrase at page 72, line 1 with the following phrase:

Ala Thr Lys Lys Asn Gly Glu Lys Leu Cys Leu Asp Leu Gln Ala Ala Leu Tyr Lys Lys Lys

-Please replace the phrase at page 73, line 1 with the following phrase:

Charge Conservation Substitution: Arg to Lys (3) (7K-RP-13-TRI,

-Please replace the phrase at page 74, line 1 with the following phrase:

Aromatic Substitution: Tyr to Trp (11) (18W-RP-13-TRI, Sequence No.

-Please replace the phrase at page 76, line 1 with the following phrase:

Charge Conservation Substitution: Asp to Glu (4) (RP-65, Sequence No.

-Please replace the phrase at page 77, line 1 with the following phrase:

The antimicrobial peptides of the invention can be utilized as 1) individual

-Please replace the phrase at page 79, line 1 with the following phrase:

E. Investigation of the Acute Toxicity of Antimicrobial Peptides in a Murine Model

-Please replace the phrase at page 80, line 1 with the following phrase:

It will be apparent from the foregoing that while particular forms of the

The following is an **Examiner's Statement of Reasons for Allowance**: The following references are related to the claimed invention. Kupsch *et al.* (The EMBO Journal 12, 641-650, 1993) disclose one member of variable opacity (Opa) outer membrane proteins, OPA 65 has 236 amino acids and comprises a sequence of ARYRKWK. Darveau *et al.* (U. S. Patent 5,409,898) disclose cationic oligopeptides having at least 8 to 11 amino acids in length and having an amino acid sequence of aa1-Leu-Tyr-Lys-Lys-aa2-aa2-Lys-Lys-Leu-Leu-aa3-aa4-X can form amphipathic alpha helix, e.g., Ala-Leu-Tyr-Lys-Lys-Leu-Leu-Lys-Lys-Leu-Leu-Lys-Ser-Ala-Lys-Lys-Leu-Gly, wherein the helix formed can be either left or right handed and can contain non-protein amino acids such as alpha, alpha-dialkyl amino acids, which has α helical amphiphilic structure and antibacterial activity. However, either Kupsch *et al.* or Darveau *et al.* do not teach or suggest that an antimicrobial peptide of 13 to 74 amino acids having a 7 amino acid core sequence (aa1-aa2-aa3-aa4-aa5-aa6-aa7) with aa1 being Ala, Lys or Gly, aa2 being Leu or Arg, aa3 being Tyr, aa4 and aa5 being Lys, Arg, or His, and one of aa6 and aa7 being Phe, Trp or Tyr such that when aa6 is Phe, aa7 is Lys, Arg or His, when aa6 is Trp, aa7 is Lys, and when aa7 is Phe, aa6 is Leu; or a modified antimicrobial peptide with modified amino acids in the core sequence and retaining antimicrobial activity, wherein the modified amino acids are N-epsilon-monomethyl-lysine, beta-branched amino acids, N-methyl amino acids, alpha, beta-dehydro amino acids or fluorinated amino acids. Yeaman *et al.* (U. S. Patent 6,743,769) disclose an antimicrobial peptide comprising the amino acid sequence of SEQ ID NO:3, 10, 13 or 14. Yeaman *et al.* (U. S. Patent 7,067,621) disclose a context-activating peptide comprising the amino acid sequence of SEQ ID NO:1, 2, 3 or 4, which contains the core sequence of Ala-Leu-Tyr-Lys-Lys-Phe-Lys, where SEQ ID NO:1 (33 amino acids), 2 (36 amino acids) and 4 (39 amino acids) of the patent comprises the instant sequence of SEQ ID NO:3 (18 amino acids). An obviousness-type double patenting rejection was made against these two patents. Terminal disclaimers were filed in the instant application over the two patents, and the obviousness-type double patenting rejection was withdrawn. Therefore, the claims are allowable over the art of record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached at 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Chih-Min Kam/
Primary Examiner, Art Unit 1656

CMK
June 8, 2010